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(19) (CA) **CANADIAN PATENT** (12)

(54) 9-Oxo-13,18-Prostadienoic Acid Derivatives and Process for Their Preparation

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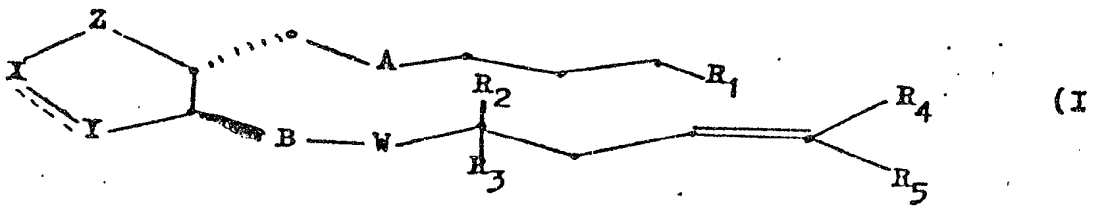
Abstract

9-oxo-13,18-prostadienoic acid derivatives and process for their preparation

A (13E)-(8R,11R,12R)-11-15-dihydroxy-9-oxo-13,18-prostadienoic acid which is substituted at the 16-position by one or two methyl groups and at the 19-position by one methyl group, or a salt thereof, is provided by the present invention. Such prostenoic acid derivatives have been found to exhibit such a therapeutic effectiveness that the amount of active substance administered to a patient can be reduced significantly in comparison with commercial preparations already available.

The present invention relates to 9-oxo-13,18-prostadienoic acid derivatives, including the physiologically tolerable salts thereof, a process for their preparation and pharmaceutical compositions containing them.

German Offenlegungsschrift No. 26 35 985 describes and claims prostanoic acid derivatives of the general formula



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in which R_1 represents a $-\overset{\overset{O}{\|}}{C}-R_6$ or $-C(R_7)(R_8)-OR_9$ group in which R_6 represents a hydroxyl group, a straight-chain or branched alkoxy group having from 1 to 10 carbon atoms, a substituted or unsubstituted aryloxy group, a $O-CH_2-U-V$ group wherein U represents a direct bond, a carbonyl group or a carbonyloxy group and V represents a phenyl ring substituted by one or more phenyl groups, alkoxy groups having 1 or 2 carbon atoms, or halogen atoms, preferably bromine atoms, or represents an NHR_{10} group in which R_{10} represents an alkyl or aryl group or an acid radical of an organic carboxylic or sulphonic acid having from 1 to 15 carbon atoms, R_7 and R_8 represent hydrogen atoms or alkyl groups having from 1 to 4 carbon atoms and R_9 either represents an acid radical of an organic carboxylic or sulphonic acid having from 1 to 15 carbon atoms or of an inorganic acid or represents a $-\overset{\overset{O}{\|}}{C}-NHR_{10}$ group wherein R_{10} has the meaning given above,

A represents a $-CH_2-CH_2$ or a cis- or trans-CH=CH- group, B represents a $-CH_2-CH_2-$, a trans-CH=CH-, a $C\equiv C-$ group or a

$-CH-CH-$ group wherein the methylene group may be in the α- or CH_2

β-position, W represents a free or functionally modified hydroxymethylene group, a free or functionally modified carbonyl group of a $-\overset{R_{11}}{\underset{OH}{C}}-$ group wherein R_{11} represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms and the OH group may be in the α- or β-position and may be functionally modified, Z represents a carbonyl or hydroxymethylene group that may be free or functionally modified, X...Y represents $-CH_2-\underset{R_{12}}{CH}-$ or $-CH_2-\overset{O}{C}-$ if Z represents a free or functionally modified hydroxymethylene group, or represents $-CH_2-\underset{R_{12}}{CH}-$ or $-CH=CH-$ if Z represents a

free or functionally modified carbonyl group, wherein the radical R_{12} represents a hydrogen atom, a methyl group, a cyanide group or a free or functionally modified hydroxy group,

R_2 represents a hydrogen atom or an alkyl group,

R_3 represents a hydrogen atom or an alkyl group,

R_4 and R_5 are the same and each represents a methyl group or

R_4 represents a chlorine atom and R_5 represents a methyl group or

R_5 represents a chlorine atom and R_4 represents a methyl group,

and if R_6 represents a hydroxy group, the physiologically tolerable salts thereof with bases.

The compounds possess valuable therapeutic properties and are distinguished especially by the fact that they are capable of inducing menstruation or terminating a pregnancy after a single intrauterine administration. They are also suitable for synchronising the sexual cycle in female mammals such as apes, cattle, pigs, sheep etc.. The prostaglandin derivatives described in German Offenlegungsschrift No. 26 35 98 have a strongly contractive action on the uterus and also a luteolytic action, that is to say lower dosages are required to induce abortion than is the case with the corresponding natural prostaglandins. Also, with natural prostaglandins, the desired, main actions are usually accompanied by undesirable side effects which considerably diminish the quality of the main action.

We have found that certain of the prostadienoic acids exhibit such outstanding properties as an abortifacient that, when used, the dosage can be reduced by a multiple in comparison with customary commercial preparations (for example, sulproston), as a result of which undesirable side effects are, of course, even more strongly repressed. When compared with compounds, mentioned in German Offenlegungsschift No. 26 35 985, we have found the compounds of the present invention to possess greater relative activity of, at least, in the range of from 10 to 100.

The present invention provides a (13E)-(8R, 11R,12R)-11, 15-dihydroxy-9-oxo-13, 18-prostadienoic acid which is substituted at the 16-position by one or two methyl groups and at the 19-position by one methyl group.

The hydroxy group at the 15-position and the methyl group at the 16-position may be in any suitable configuration. Preferably the 15-hydroxy group has an S-configuration when the 16-methyl group has an RS-configuration. When the compound is disubstituted in the 16-position by a methyl group, the 15-hydroxy group preferably has an R-configuration.

The present invention also provides a salt of a compound of the invention, especially a physiologically tolerable salt thereof.

None of the compounds of the present invention are specifically described in German Offenlegungsschrift No. 26 35 985. Compounds in which A represents a $-CH_2-CH_2-$ group are not distinguished from the other compounds in which A represents a cis-CH=CH- group in that document.

Suitable for the salt formation are all inorganic and organic bases such as those known to the man skilled in the art for the formation of physiologically tolerable salts. There may be mentioned, by way of example, alkali metal hydroxides, such as sodium or potassium hydroxide, alkaline earth metal hydroxides, such as calcium hydroxide, ammonia, amines, such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, tris(hydroxymethyl)-methylamine, etc..

The present invention further provides a process for the

preparation of a compound of the invention, or a salt thereof, which comprises reacting

(8R,9S,11R,12S) -9-benzoyloxy-13-oxo-11-(tetrahydropyran-2-yloxy)-14,15,16,17,18,19,20-heptanorprostanoic methyl ester

with either

2-(1,4-dimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester

or

2-(1,1,4-trimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester and then whichever of the following steps are necessary or desired are carried out in any suitable order

a) a free hydroxy group is protected

b) a protected hydroxy group is converted to a free hydroxy group

c) a 15-oxo group is reduced

d) a 9-oxo group is reduced

e) a 9-hydroxy group is oxidised

f) an acid is converted into a salt

g) a salt is converted into an acid

h) a salt is converted into another salt

i) a mixture of racemates is separated.

The reaction of (8R,9S,11R,12S)-9-benzoyloxy-13-oxo-11-(tetrahydropyran-2-yloxy)-14,15,16,17,18,19,20-heptanorprostanoic acid methyl ester with 2-(1,4-di-or 2-(1,1,4-tri-methyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester may be carried out in a

manner known per se at a temperature in the range of from 0°C to 100°C, preferably from 20°C to 80°C, in an aprotic solvent, such as, for example, dimethyl sulphoxide, dimethylformamide, benzene, toluene, xylene, diethyl ether, tetrahydrofuran, dioxan, chloroform, methylene chloride and dimethoxyethane.

The preparation of the compounds 2-(1,4-di- and 2-(1,1,4-tri-methyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester may be carried out according to methods known per se, as have been described in German Offenlegungsschrift No. 26 35 985.

The oxidation of the 9-hydroxy group may also be carried out according to methods known per se with the customary oxidising agents. For example, the oxidation can be carried out with the 11- and 15-hydroxy groups being temporarily protected, for example by silylation with Jones reagent (Chem. Comm. 1972), 1120).

Freeing of functionally modified hydroxy groups is suitably carried out according to known methods. For example, the splitting off of hydroxy-protecting groups, such as, for example, the tetrahydropyranyl radical, may be carried out in an aqueous solution of an organic acid, such as, for example, oxalic acid, acetic acid and propionic acid inter alia, or in an aqueous solution of an inorganic acid, such as, for example hydrochloric acid. To improve solubility, a water-miscible inert organic solvent is advantageously added. Suitable organic solvents are, for example alcohols such as methanol and ethanol, ethers, such as di-methoxyethane, dioxan and tetrahydrofuran, and acetone. Preferably tetrahydropyran is used. The splitting-off operation is preferably

carried out at a temperature in the range of from 20°C to 80°C.

Hydrolysis of the acyl groups is carried out, for example with alkali metal carbonates or hydroxides or with alkaline earth metal carbonates or hydroxides in an alcohol or in an aqueous solution of an alcohol. Alcohols that come into consideration are aliphatic alcohols, such as, for example, methanol, ethanol and butanol, preferably methanol. As alkali metal carbonates and hydroxides both potassium and sodium salts are suitable but potassium salts are preferred. Suitable alkaline earth metal carbonates and hydroxides are, for example, calcium carbonate, calcium hydroxide and barium carbonate. The reaction is suitably carried out at a temperature in the range of from -10°C to +70°C, preferably at +25°C.

The compounds of the invention may be converted into salts with suitable amount of the corresponding inorganic bases with neutralisation taking place. For example, upon dissolving the prostadienoic acid in water containing the stoichiometric amount of the base, after evaporating off the water or after adding a water-miscible solvent, for example alcohol or acetone, a solid inorganic salt is obtained.

For the preparation of an amine salt, which is suitably carried out in customary manner, the prostadienoic acid is, for example, dissolved in a suitable solvent, for example ethanol, acetone, diethyl ether or benzene, and at least the stoichiometric amount of the amine is added to that solution. In so doing, an amine salt is usually obtained in solid form or is

isolated in customary manner after evaporation of the solvent.

Other steps in the process of the invention may be carried out by known methods.

The good dissociation of action of the compounds according to the invention may be demonstrated in tests on other non-striated organs, such as, for example, the ileum of guinea pigs or the isolated trachaea of rabbits, in which considerably lower stimulation than that produced by the natural prostaglandins has been observed by us.

Prostadienoic acid derivatives of the present invention have been found to exhibit a bronchodilative action on the isolated trachaea of rabbits in vitro and greatly inhibit gastic acid secretion and to have a regulatory action in the case of heart rhythm disorders. The compounds of the invention furthermore reduce blood pressure and have a diuretic action. The trimethyl substituted compounds of the invention have also been found to have a cytoprotective action on the stomach.

For medicinal use, the active substance may be converted into a form suitable for inhalation or for oral or parenteral administration.

For inhalation, aerosol or spray solutions are advantageously used.

For oral administration, tablets, dragées or capsules for example, are suitable.

For parenteral administration, sterile, injectable, aqueous or oily solutions may be used.

Accordingly, the present invention provides a pharamceutical preparation comprising a compound of the present invention, or a physiologically tolerable salt thereof, in admixture of conjunction with a pharmaceutically suitable carrier.

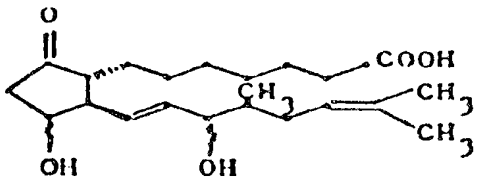
Preferbly the preparation is in unit dosage form. Depending upon the mode of administration, for example vaginal, extraamnial, intramuscular or intravenous, the unit dosage is suitably in the range of from 0.25 g to 50 mg.

The active substances of the invention may be used in combination with the auxiliaries known and customary in galenical pharmacy, for example for the production of preparations for inducing an abortion, for controlling the menstrual cycle or for inducing labour. For this purpose, sterile aqueous solutions containing in the range of from 0.0001 to 10 g/ml of the active solution. For the preparation of aqueous isotonic solutions, the acid and salts are especially suitable. To increase solubility, alcohols, such as ethanol and propylene glycol, may be added. In addition, suppositories for intravaginal administration can readily be prepared.

The following Examples illustrate the invention. Unless otherwise indicated, the percentages and proportions in the Examples are given on a volume basis. The abbreviations "DIBAH" and "TLC" are used in the Examples to indicate "diisobutylaluminium hydride" and "thin layer chromatography" respectively.

Example 1

(13E)-(8R,11R,12R,15S,16RS)-11,15-dihydroxy-16,19-dimethyl-9-oxo-13,18-prostadienoic acid



a) 2-ethoxycarbonyl-2,5-dimethyl-4-hexenoic acid ethyl ester

36.1 g of sodium (cut into small pieces) were placed in a three-necked flask equipped with a reflux condenser, dropping funnel and stirrer. 800 ml of absolute ethanol were added dropwise thereto rapidly enough to keep the solution boiling briskly. 269.6 g of freshly distilled methylmalonic acid diethyl ester were added dropwise to the hot alcoholate solution, the mixture was stirred for 1/2 hour at 60°C and then 241.7 g of dimethylallyl bromide were added dropwise thereto. After stirring for one hour while heating, the precipitated sodium bromide was filtered off, the precipitate was washed and the filtrate concentrated. The residue was taken up in ether, washed neutral with saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a rotary evaporator. The residue remaining after evaporation was fractionated using an oil pump. 266 g of the title compound ($b.p._{.7}$ = 97-112°C) were obtained.

IR (film): 1735, 1245, 1025, 860/cm.

b) 2-carboxy-2,5-dimethyl-4-hexenoic acid

223.8 g of the diester obtained in a) were heated under reflux for 4 hours together with 181 g of potassium hydroxide in 235 ml of water and 450 ml of ethanol. The ethanol was subsequently removed in a rotary evaporator, the residue was dissolved in 235 ml of water and, while cooling with ice, concentrated hydrochloric acid was added dropwise until a pH of 1 was reached. The precipitate (m.p. 162-

166°C) was collected, washed with water and used in the next step without further purification.
IR (KBr): 1700, 1230, 840/cm.

c) 2,5-dimethyl-4-hexenoic acid

The dicarboxylic acid obtained in the preceding reaction step was maintained at 210°C for 4 hours at normal pressure and then for one hour at 75 torr in a distillation apparatus. The product was then distilled in vacuo. 68 g of the title compound ($b.p._5$ = 90-106°C; $b.p._1$ = 67-70°C) were obtained.
IR (film): 1705, 1220, 810/cm.

d) 2,5-dimethyl-4-hexenoic acid methyl ester

Ethereal diazomethane was added to the 68 g of carboxylic acid obtained according to the method described above, until no more nitrogen was evolved upon adding the reagent and the yellow colour of the reaction solution remained unchanged. The solvent was then removed in vacuo and the residue fractionated. 62.3 g of the title compond ($b.p._{3.5-6}$ = 32-35°C) were obtained.
IR (film): 1735, 1160, 1050, 820/cm.

e) 2,5-dimethyl-4-hexenoic acid ethyl ester

85.3 g of 2-ethoxycarbonyl-2,5-dimethyl-4-hexenoic acid ethyl ester were dissolved in 645 ml of dimethyl sulphoxide, and 29.7 g of lithium chloride and 6.3 ml of distilled water were added in succession. The reaction mixture was then heated at 200°C for a total of 13 hours and subsequently, after being left to cool, was poured onto 1 litre of ice-water. The aqueous phase was extracted three times with 500 ml of methylene chloride each time. The combined organic extracts were then washed twice with water, dried over magnesium sulphate, concentrated in a rotary evaporator and distilled in vacuo. 53.1 g of the title compound ($b.p._{13}$ = 75-78°C) were isolated.

IR (film): 1735, 1160, 1050/cm.

f) 2-(1,4-dimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester

274.7 ml of a 1.61M butyllithium solution in hexane was added dropwise under argon at -60°C to a solution of 59 g of methanephosphonic acid dimethyl ester in 400 ml of absolute tetrahydrofuran. After stirring for 15 minutes, a solution of 34.05 g of 2,5-dimethyl-4-hexenoic acid ethyl ester in 100 ml of absolute tetrahydrofuran was added dropwise. The reaction mixture was left to warm to room temperature

over a period of four hours and was then stirred for a further 3 hours. 26.5 ml of glacial acetic acid were then added and the mixture was concentrated in vacuo. The residue was taken up in ether/water, solid sodium chloride was added to the aqueous phase and extraction with ether was carried out. The combined organic phases were dried over magnesium sulphate and concentrated in a rotary evaporator. The residue remaining after evaporation was purified by column chromatography over silica gel with hexane/50-100% ethyl acetate as eluant. 32 g of the desired compound were obtained.
IR (film): 1710, 1260, 1030/cm.

g) (1S,5R,6S,7R)-6-[(tert.-butyldimethylsilyloxy)-methyl]-7-benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one

A solution of 9.9 g of dimethyl-tert.-butyl-chlorosilane in 40 ml of absolute dimethylformamide and 9.35 g of imidazole were added to a solution of 13.8 g of (1S,5R,6R,7R)-6-hydroxy-methyl-7-benzoyloxy-2-oxabicyclo [3.3.0]octan-3-one in 30 ml of absolute dimethylformamide. After stirring for 2 hours at room temperature and under an argon atmosphere, analytical thin-layer chromatography indicated complete reaction. The reaction mixture was

diluted with 850 ml of ether, washed with approximately 60 ml of saturated sodium bicarbonate solution and saturated sodium chloride solution and then dried over magnesium sulphate. The residue remaining after concentration by evaporation may, if desired, be purified by column chromatography over silica gel with ether as eluant. 17.8 g of the title compound (m.p. = 74-75°C after crystallisation from pentane/ether) were obtained.
IR: 1775, 1715, 1600, 1580, 1275, 1255, 840, 790, 720/cm.

h) (1S,5R,6S,7R)-6-[(tert.-butyldimethylsilyloxy)-methyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one

A solution of 17.3 g of the benzoate obtained in the preceding reaction step in 200 ml of absolute methanol was stirred with 6.5 g of dry potassium carbonate at room temperature under argon. After two hours, analytical thin-layer chromatography indicated complete reaction. Then, at 0°C, 500 ml of 0.1N hydrochloric acid were added dropwise to the reaction mixture, the whole was stirred for 15 minutes at room temperature, concentrated in vacuo and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution and dried over magnesium sulphate. The residue remaining after concentration by evaporation was purified by column chromatography over silica gel with hexane/50-100% ether as eluant. 9.1 g of the desired compound (m.p.: 57-58.5°C) were obtained.

IR (film): 1775, 1255, 840, 790/cm.

i) (1S,5R,6S,7R)-6-[(tert.-butyldimethylsilyloxy)-methyl]-7-(tetrahydropyran-2-yloxy)-2-oxabicyclo[3.3.0]octan-3-one

A solution of 15.8 g of alcohol obtained according to the method described above in 300 ml of distilled methylene chloride was stirred with 7.5 ml of dihydropyran freshly distilled using potassium hydroxide, and 1.38 g of pyridine-p-toluenesulphonate for 14 hours at room temperature. After concentrating the reaction solution at room temperature, it was diluted with ether and washed with semi-saturated sodium chloride solution. The organic solution was subsequently dried over magnesium sulphate and then concentrated to dryness. The product may, if desired, be purified by column chromatography over silica gel with hexane/20-50% ether as eluant. The yield was 20 g.
IR (film): 1775, 1255, 1115, 1080, 1035, 835, 775/cm.

j) (1S,3RS,5R,6S,7R)-3-hydroxy-6-[(tert.-butyl-dimethylsilyloxy)-methyl]-7-(tetrahydropyran-2-yloxy)-2-oxabicyclo[3.3.0]octane

20 ml of a 20% DIBAH solution in toluene were added dropwise under argon in the course of 15 minutes to

a solution, cooled to -70°C, of 5.4 g of the lactone obtained in the preceding reaction step in 200 ml of absolute toluene. After stirring for approximately 5 minutes, 1.2ml of isopropanol were added at the same temperature until the formation of foam ceased. The reaction solution was left to warm to 0°C, 16 ml of water were added, and the mixture was stirred for 10 minutes and filtered over a frit. The precipitate was washed with ethyl acetate. The organic phase was washed three times with saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a rotary evaporator. The resulting product (5.41 g) was used in the next reaction step without further purification.

k) (5Z)-(8R,9S,11R,12S)-9-hydroxy-11-(tetrahydropyran-2-yloxy)-13-(tert.-butyldimethylsilyloxy)-14,15,16,17,18,19,20-heptanor-5-prostenoic acid

104.6 ml of a solution of methanesulphinylmethyl sodium in absolute dimethyl sulphoxide (prepared by dissolving 6 g of 50% by weight sodium hydride suspension in 120 ml of absolute dimethyl sulphoxide at a maximum of 70°C) were added dropwise at 15°C to a solution of 25.67 g of 4-carboxybutyltriphenylphosphonium bromide (previously dried at 70-80°C using an oil pump) in 80 ml of absolute dimethyl sulphoxide. This ylene solution was stirred for 30 minutes at room temperature and then, while cooling with water, added dropwise in the course of 15 minutes to a solution of

5.41 g of the lactol obtained in the preceding reaction step in 50 ml of absolute dimethyl sulphoxide. The reaction mixture was then stirred for four hours at 35-40°C under argon. (50-100 ml of absolute tetrahydrofuran may optionally be added to the reaction solution).

For working up, the reaction mixture was poured onto ice-water, extracted three times with ether, and the aqueous phase was acidified to pH 4 with 10% by weight citric acid solution and extracted three times with a 1/1 mixture of ether/hexane. Extraction was then carried out another three times by shaking with methylene chloride. On the basis of analytical thin-layer chromatography, the methylene chloride phase was discarded, but the other two organic phases were combined, dried over magnesium sulphate, filtered and concentrated in a rotary evaporator. The residue was purified by column chromatography over silica gel with hexane/70-100% ether as eluant.

4.32 g of the carboxylic acid were obtained.
IR (film): 3440 (broad), 3220-2500, 1725, 1700, 1250, 1100, 1020, 830, 770/cm.

l) (5Z)-(8R,9S,11R,12S)-9-hydroxy-11-(tetrahydropyran-2-yloxy)-13-(tert.-butyldimethylsilyloxy)-14,15,16,17,18,19,20-heptanor-5-prostenoic acid methyl ester

Preparation with diazomethane:

The 4.32 g of carboxylic acid obtained in k) were

dissolved in 20 ml of methylene chloride, and ethereal diazomethane solution was added until the evolution of gas had ceased and the yellow colour of the solution remained unchanged. After drawing off the excess diazomethane using a water-jet vacuum, the reaction solution was concentrated to dryness in a rotary evaporator. 4.3 g of the desired carboxylic acid methyl ester were obtained.

Preparation with iodomethane:

75 ml of N-ethyldiisopropylamine and 150 ml of iodomethane in 200 ml of acetonitrile were added dropwise at room temperature in the course of 2 hours to a solution of 32.5 g of the carboxylic acid obtained in k) in 450 ml of acetonitrile. Stirring was carried out for one hour, then, after TLC examination, the precipitate was suction-filtered and washed with ethyl acetate, and the organic phase was shaken in succession with sodium bisulphate, sodium bicarbonate and sodium chloride solutions. After drying over magnesium sulphate, the mixture was concentrated to dryness in a rotary evaporator and the residue was purified by column chromatography over silica gel with hexane/50-100% ether as eluant. 32.3 g of the title compound were obtained.

IR (film): 3420 (broad), 1740, 1255, 1120, 1030, 840, 780/cm.

m) (5Z)-(8R,9S,11R,12S)-9-benzoyloxy-11-(tetrahydropyran-2-yloxy)-13-(tert.-butyldimethylsilyloxy)-14,15,16,17,18,19,20-heptanor-5-prostenoic acid methyl ester

2.32 ml of distilled benzoyl chloride were added dropwise while stirring at room temperature to a solution of 4.7 g of the 9-hydroxy compound obtained in 1) in 70 ml of pyridine. After stirring for two hours under an argon atmosphere, 1.8 ml of water were added to the reaction solution, the mixture was stirred for a further hour and then concentrated at 30°C and 1 torr using an oil pump. The residue was taken up in a two-phase mixture of ether/water, washed with sodium bicarbonate and saturated sodium chloride solution, dried over magnesium sulphate and concentrated to dryness in vacuo. After column chromatography of the evaporation residue over silica gel with hexane/30-50% ethyl acetate as eluant, 5.11 g of the title compound were obtained as a colourless oil.
IR (film): 1745, 1720, 1605, 1590, 1280, 1260, 1120, 1030, 840, 780, 710/cm.

n) (8R,9S,11R,12S)-9-benzoyloxy-11-(tetrahydropyran-2-yloxy)-13-(tert.-butyldimethylsilyloxy)-14,15,16,17,18,19,20-heptanorprostanoic acid methyl ester

1.23 g of 10% by weight palladium-on-carbon were added to

a solution of 12.3 g of the unsaturated compound obtained in m) in 160 ml of ethyl acetate and the mixture was hydrogenated in a shaking apparatus at room temperature and under a slight hydrogen overpressure. When 640 ml of hydrogen had been absorbed, the solvent was removed in vacuo, the residue was taken up in 40 ml of ether, the organic phase was washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated to dryness in a rotary evaporator. 12.1 g of the title compound were obtained.

IR (film): 1740, 1720, 1600, 1580, 1275, 1255, 1115, 1070, 1025, 835, 780, 710/cm.

o) (8R,9S,11R,12S)-9-benzoyloxy-11-(tetrahydropyran-2-yloxy)-13-hydroxy-14,15,16,17,18,19,20-heptanorprostanoic acid methyl ester

16.11 ml of a 2M tetrabutylammonium fluoride solution in tetrahydrofuran were added, while cooling with ice, to a solution of 6.94 g of the compound obtained in the preceding reaction step in 110 ml of absolute tetrahydrofuran. After stirring for 12 hours under an argon atmosphere, the reaction mixture was diluted with 1.3 litres of ether, washed neutral with saturated sodium chloride solution and the washing solution was subsequently extracted twice with ether. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. The residue was purified by column chromatography over

silica gel with ethyl acetate as eluant. 5.54 g of the desired compound were obtained as a colourless oil.
IR (film): 3460 (broad), 1735, 1715, 1600, 1580, 1275, 1115, 1070, 1025, 710/cm.

p) (8R,9S,11R,12S)-9-benzoyloxy-13-oxo-11-(tetrahydropyran-2-yloxy)-14,15,16,17,18,19,20-heptanorprostanoic acid methyl ester

A solution of 5.54 g of the alcohol obtained according to the method described above in 56 ml of absolute methylene chloride was added dropwise at 5-10°C in the course of 20 minutes to a suspension of 18.7 g of Collins reagent in 170 ml of absolute methylene chloride. After stirring the reaction mixture for one hour in an argon atmosphere, 500 ml of a 1/1 mixture of ether and pentane were added and decanting was carried out. The flask was washed two more times with 500 ml of the same mixture as mentioned above, each time. The combined organic phases were then shaken three times with 50 ml of 5% by weight sodium carbonate solution each time and three times with 50 ml of 5% sulphuric acid each time and were then washed neutral with saturated sodium chloride solution. After drying over magnesium sulphate, the mixture was concentrated to dryness and the residue was filtered over a column of silica gel (50 g; eluant: ethyl acetate/hexane = 2/8). 4.6 g of the desired aldehyde were obtained.
IR (film): 2720, 1735, 1715, 1600, 1580, 1275, 1115, 1070, 1025, 715/cm.

q) (13E)-(8R,9S,11R,12R,16RS)-9-benzoyloxy-16,19-dimethyl-15-oxo-11-(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

2.48 g of the phosphonate obtained according to f), dissolved in 30 ml of absolute dimethoxyethane, were added dropwise at room temperature under argon to a suspension of 0.48 g of 50% by weight sodium hydride (suspended in oil) in 60 ml of dimethoxyethane freshly distilled using lithium aluminium hydride. After the addition of 0.43 g of lithium chloride (previously dried in a vacuum cupboard for 2 hours at 50°C), the reaction mixture was stirred for 2 hours at room temperature. The suspension was subsequently cooled to -20°C and 4.61 g of the aldehyde obtained according to p), dissolved in 90 ml of absolute dimethoxyethane, were added dropwise. The temperature was then allowed to increase from -20°C to 0°C in the course of 5 hours and to 5°C in the course of 1.5 hours in order then to stir the reaction solution for a further 3 hours at room temperature. At -10°C, there were then added dropwise 1 ml of glacial acetic acid and approximately 100 ml of water. The phases were separated, the aqueous phase was extracted 5 times with ether, and the organic phases were combined and washed with 4% by weight sodium bicarbonate and saturated sodium chloride solutions. After drying over magnesium sulphate, the mixture was concentrated to dryness in a rotary evaporator. The residue was subjected to purification by column chromatography over silica gel

with ethyl acetate/hexane = 1/1 as eluant. 5.78 g of the title compound were obtained.

IR (film): 1740, 1720, 1695, 1670, 1625, 1600, 1580, 1270, 1105, 1060, 1025, 705/cm.

r) (13E)-(8R,9S,11R,12R,15R,16RS)-9-benzoyloxy-16,19-dimethyl-15-hydroxy-11-(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

2.37 g of sodium borohydride were added in portions to a solution, cooled to -40°C, of 5.78 g of the ketone obtained in the preceding reaction step in 115 ml of absolute methanol. After stirring for one hour at -40°C, 5.09 ml of glacial acetic acid were added dropwise to the reaction solution likewise at -40°C. After removing the solvent in a rotary evaporator, methylene chloride/water were added to the residue, solid sodium chloride was added to the separated aqueous phase and the mixture was extracted twice with methylene chloride. The combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The isomers were separated by repeated column chromatography several times over silica gel with hexane/20-100% ethyl acetate as eluant. 2.11 g of the title compound were isolated as the least polar product.

IR (film): 3400 (broad), 1740, 1720, 1600, 1580, 1275, 1120, 1030, 1020, 710/cm.

s) (13E)-(8R,9S,11R,12R,15R,16RS)-9-benzoyloxy-16,19-dimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

0.49 ml of dihydropyran (freshly distilled using potassium hydroxide) and 9.7 mg of p-toluenesulphonic acid were added at ice-bath temperature to a solution of 2.11 g of the alcohol obtained according to r) in 60 ml of absolute methylene chloride, the mixture was stirred for 55 minutes at 0°C and, having diluted the reaction solution with methylene chloride, it was extracted with saturated sodium bicarbonate solution and water. The organic phase was dried over magnesium sulphate and concentrated in vacuo. The residue was purified by column chromatography over silica gel with ethyl acetate/hexane = 1/2 as eluant. 2.3 g of the desired compound were obtained.

IR (film): 1740, 1720, 1605, 1585, 1275, 1115, 1080, 1025, 715/cm.

t) (13E)-(8R,9S,11R,12R,15R,16RS)-9-hydroxy-16,19-dimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid

20.6 ml of 2N potassium hydroxide solution were added to a solution of 2.3 g of the benzoate obtained according to s) in 70 ml of methanol and the mixture was stirred for 31 hours at room temperature. The reaction mixture was subsequently concentrated in a rotary

evaporator, and the residue was taken up in a little water and extracted twice with 150 ml of an ether/pentane mixture each time. The aqueous phase was acidified to a pH of 5 with citric acid and extracted three times with 150 ml of ethyl acetate each time. The combined organic phases were washed neutral with saturated sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The residue was purified by column chromatography over silica gel with hexane/50-100% ethyl acetate as eluant. 1.62 g of the title compound were obtained.
IR (film): 3460, 2730, 2660, 1730, 1710, 1130, 1110, 1075, 1020, 810/cm.

u) (13E)-(8R,11R,12R,15R,16RS)-9-oxo-16,19-dimethyl-11,15-bis (tetrahydropyran-2-yloxy)-13, 18-prostadienoic acid

0.46 ml of Jones reagent was added to a solution, cooled to -20°C, of 360 mg of the alcohol obtained according to t) in 7 ml of acetone and the mixture was stirred at that temperature for 45 minutes. 0.6 ml of isopropanol was then added, the mixture was stirred for a further 10 minutes, diluted with cold ether and washed three times with cold saturated sodium chloride solution, and the organic phase was dried over magnesium sulphate and concentrated in vacuo. After filtration over a Sep-Pack prepared column, 327 mg of the title compound were obtained.
IR (film): 2730, 2660, 1740, 1710, 1110, 1075, 1025, 810/cm.

v) (13E)-(8R,11R,12R,15R,16RS)-9-oxo-11,15-dihydroxy-16,19-dimethyl-13,18-prostadienoic acid

The 327 mg obtained according to the method described above in u) were stirred at room temperature for 26 hours in 7 ml of a mixture of glacial acetic acid/water/tetrahydrofuran (65/35/10). The whole was then concentrated several times with benzene in an oil pump vacuum at room temperature. The residue was purified by column chromatography over silica gel with ethyl acetate/0-10% methanol as eluant. 68 mg of the title compound were obtained.

IR (film): 3420, 2730, 2670, 1735, 1710, 1075, 975/cm.

w) (13E)-(8R,9S,11R,12R,15S,16RS)-9-benzoyloxy-16,19-dimethyl-15-hydroxy-11-(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

In the sodium borohydride reduction of the ketone according to r), in addition to the 2.11 g of β-alcohol and 0.27 g of an α/β mixture, 2.67 g of the title compound were eluted from the column as a more polar product.

IR (film): 3400 (broad), 1740, 1720, 1600, 1580, 1275, 1120, 1030, 1020, 710/cm.

x) (13E)-(8R,9S,11R,12R,15S,16RS)-9-benzoyloxy-16,19-dimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

Analogously to the method described in s) for the preparation of the 15β-isomer, 2.96 g of the title compound were obtained as a colourless oil by reacting 2.67 g of the alcohol obtained in the preceding reaction step with 0.62 ml of dihydropyran and 12.3 mg of p-toluenesulphonic acid (reaction time: 75 minutes) and after column chromatography over silica gel with ethyl acetate/hexane = 1/3 as eluant.

IR (film): 1740, 1720, 1600, 1585, 1275, 1115, 1075, 1025, 715/cm.

y) (13E)-(8R,9S,11R,12R,15S,16RS)-9-hydroxy-16,19-dimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid

Analogously to the method described for the preparation of the 15β-isomer in t), 2.22 g of the title compound were obtained by reacting 2.96 g of the compound of x) with 26.5 ml of 2N potassium hydroxide solution and after column chromatography over silica gel with hexane/50-100% ethyl acetate as eluant.

IR (film): 3450, 2730, 2660, 1730, 1710, 1130, 1110, 1075, 1020, 810/cm.

z) (13E)-(8R,11R,12R,15S,16RS)-9-oxo-16,19-dimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid

360 mg of the alcohol obtained in the preceding reaction step were reacted analogously to the method described for the preparation of the corresponding 15β-isomer in u). 326 mg of the title compound were obtained.

IR (film): 2730, 2670, 1740, 1710, 1105, 1070, 1020, 810/cm.

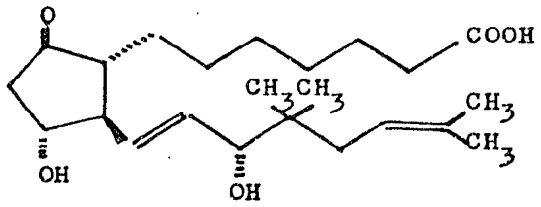
(13E)-(8R,11R,12R,15S,16RS)-9-oxo-11,15-dihydroxy-16,19-dimethyl-13,18-prostadienoic acid

Analogously to the method described for the synthesis of the 15β-isomer in v), 54 mg of the title compound of Example 1) were obtained by reacting 326 mg of the compound obtained in the preceding reaction step.

IR (film): 3400, 2730, 2660, 1740, 1710, 1075, 975/cm.

Example 2

(13E)-(8R,11R,12R,15R)-11,15-dihydroxy-16,16,19-trimethyl-9-oxo-13,18-prostadienoic acid



a) 2,2,5-trimethyl-4-hexenoic acid ethyl ester

610 ml of a 1.64N butyllithium solution in hexane were added dropwise under argon at -20°C to a solution of 101.2 g of diisopropylamine in 125 ml of absolute tetrahydrofuran. The temperature was allowed to rise for a short time to approximately 0°C, in order then to add 116 g of isobutyric acid ethyl ester dropwise at from -50 to -60°C to the lithiumdiisopropylamide solution. The reaction solution was stirred for one hour at 0°C, then cooled to -40°C and subsequently added to a solution, maintained at -20°C, of 200 g of 4-bromo-2-methyl-2-butene (dimethylallyl bromide) in 60 ml of absolute dimethyl sulphoxide. While allowing the temperature to rise to room temperature, the reaction mixture was stirred for 60 hours and subsequently 250 ml of saturated sodium chloride solution were added. The organic phase was separated off and the aqueous phase was extracted five times with 200 ml each time of a 1/1 mixture consisting of ether and hexane. The combined organic phases were washed neutral with 0.5N hydrochloric acid and saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a rotary evaporator. The residue was

distilled in vacuo. 91.5. g of the desired ester were obtained ($b.p._{13}$=76-81°C).

IR (film): 1735, 1160, 1060, 820/cm.

b) 2,2,5-trimethyl-4-hexenoic acid methyl ester

The title compound was prepared according to the method described above for the synthesis of the corresponding ethyl ester using isobutyric acid methyl ester.

$b.p._{13}$= 72-74°C.

IR (film): 1735, 1160, 1050, 820/cm.

c) 2,2,5-trimethyl-4-hexenoic acid

The title compound was prepared according to the method described in a) above using isobutyric acid as educt and 2 equivalents of lithium diisopropylamide. $b.p._{0.2-0.4}$ = 94-100°C.

IR (film): 1705, 1220, 820/cm.

d) 2-(1,1,4-trimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester

49.5 ml of a 2.02N butyllithium solution in hexane were added dropwise under argon at -60°C to a solution of 13 g of methanephosphonic acid dimethyl ester in 160 ml of absolute tetrahydrofuran. After 15 minutes, a solution of 9.2 g of 2,2,5-trimethyl-4-hexenoic acid ethyl ester in 25 ml of absolute tetrahydrofuran was added dropwise. After 2 hours at -60°C, the reaction mixture was left to warm to room temperature in the cours of one hour, 5.72 ml of glacial acetic acid were added and the mixture was then concentrated in vacuo. The residue, a white gel-

like mass, was divided in a two-phase mixture consisting of 35 ml of water and 165 ml of ether. The organic phase was dried over magnesium sulphate and concentrated in a rotary evaporator. After the volatile side-products had been distilled off at 60°C and 0.1 torr, the residue was purified by column chromatography over silica gel with hexane/50-100% ethyl acetate as eluant. 8.6 g of the title compound were obtained.

IR (film): 1705, 1260,1030,820/cm.

e) (13E)-(8R,9S,11R,12R)-9-benzoyloxy-16,16,19-trimethyl-15-oxo-11-(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

4.05 g of the phosphonate obtained according to d) dissolved in 45 ml of absolute dimethoxyethane, were added dropwise at room temperature under argon to a suspension of 0.74 g of 505 by weight sodium hydride (suspended in oil) in 90 ml of dimethoxyethane freshly distilled using lithium aluminium hydride. After the addition of 0.66 g of lithium chloride (previously dried in a vacuum cupboard for 2 hours at 50°C), the reaction mixture was stirred for 2 hours at room temperature. The suspension was subsequently cooled to -20°C and 7.11 g of the aldehyde obtained according to Example 1p) dissolved in 140 ml of absolute dimethoxyehtane, were added dropwise. The temperature was then allowed to increase from -20°C to 15°C in the course of 5 hours in order then to stir the reaction solution for a further 19 hours at room temperature. At -10°C, there were then added

dropwise 1.6 ml of glacial acetic acid and approximately 100 ml of water. The phases were separated, the aqueous phase was extracted 5 times with ether, and the organic phases were then combined and washed with 4% by weight sodium bicarbonate and saturated sodium chloride solutions. After drying over magnesium sulphate, the mixture was concentrated to dryness in a rotary evaporator. The residue was subjected to purification by column chromatography over silica gel with hexane/150-100% ethyl acetate as eluant. 9.19 g of the title compound were obtained.

IR (film): 1740, 1720, 1695, 1670, 1625, 1600, 1580, 1270, 1105, 1060, 1030, 705/cm.

f) (13E)-(8R,9S,11R,12R,15S)-9-benzoyloxy-16,16,19-trimethyl-15-hydroxy-11-(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

3.68 g of sodium borohydride were added in portions to a solution, cooled to -40°C, of 9.19 g of the ketone obtained in the preceding reaction step in 180 ml of absolute methanol. After stirring for 3.5 hours at -40°C, 7.9 ml of glacial acetic acid were added dropwise to the reaction solution likewise at -40°C. After removing the solvent in a rotary evaporator, methylene chloride/water were added to the residue, solid sodium chloride was added to the separated aqueous phase and the mixture was extracted twice with methylene chloride. The combined organic phases were washed with saturated sodium chloride solution dried over magnesium sulphate and concentrated in vacuo. The

isomers were separated by repeated column chromatography several times over silica gel with hexane/20-40% ethyl acetate as eluant. 2.02 g of the title compound were isolated as the more polar product.
IR (film): 3400 (broad), 1740, 1720, 1600, 1580, 1275, 1120, 1030, 1025, 710/cm.

g)(13E)-(8S,9S,11R,12R,15S)-9-benzoyloxy-16,16,19-trimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

0.45 ml of dihydropyran (freshly distilled using potassium hydroxide) and 9 mg of p-toluenesulphonic acid were added at ice-bath temperature to a solution of 2 g of the alcohol obtained according to f) in 60 ml of absolute methylene chloride, the mixture was stirred for 55 minutes at 0°C and, having diluted the reaction solution with methylene chloride, it was extracted with saturated sodium bicarbonate solution and water. The organic phase was dried over magnesium sulphate and concentrated in vacuo. The residue was purified by column chromatography over silica gel with ethyl acetate/hexane = 1/2 as eluant. 2.12 g of the desired compound were obtained.
IR (film): 1740, 1720, 1605, 1585, 1275, 1115, 1080, 1025, 715/cm.

h) (13E)-(8R,9S,11R,12R,15S)-9-hydroxy-16,16,19-trimethyl-11,15-bis(tetraphydropyran-2-yloxy)-13,18-prostadienoic acid

19 ml of 2N potassium hydroxide solution were added to a solution of 2.12 g of the benzoate obtained according to g) in .

60 ml of methanol and the mixture was stirred for 26 hours at room temperature. The reaction mixture was subsequently concentrated in a rotary evaporator, and the residue was taken up in a little water and extracted twice with 150 ml of an ether/pentane mixture each time. The aqueous phase was acidified to a pH of 5 with citric acid and extracted three times with 150 ml of ethyl acetate each time. The combined organic phases were washed neutral with saturated sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The residue was purified by column chromatography over silica gel with hexane/50-100% ethyl acetate as eluant. 1.43 g of the title compound were obtained.

IR (film): 3460, 2730, 2660, 1730, 1710, 1130, 1110, 1075, 1025, 810/cm.

i) (13E)-(8R,11R,12R,15S)-9-oxo-16,16,19-trimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid

0.63 ml of Jones reagent was added to a solution, cooled to -20°C, of 500 mg of the alcohol obtained according to h) in 10 ml of acetone and the mixture was stirred at that temperature for 45 minutes. 0.8 ml of isopropanol was then added, the mixture was stirred for a further 10 minutes, diluted with cold ether and washed three times with cold saturated sodium chloride solution, and the organic phase was dried over magnesium sulphate and concentrated in vacuo. After filtration over a Sep-Pack prepared column, 442 mg of the title compound

were obtained.

IR (film): 2730, 2660, 1740, 1710, 1105, 1070, 1025, 810/cm.

j) (13E)-(8R,11R,12R,15S)-11,15-dihydroxy-16,16,19-trimethyl-9-oxo-13,18-prostadienoic acid

The 442 mg obtained according to the method described above in i) were stirred at room temperature for 24 hours in 9 ml of glacial acetic acid/water/tetrahydrofuran (65/35/10). The whole was then concentrated several times with benzene in an oil pump vacuum at room temperature. The residue was purified by column chromatography over silica gel with ethyl acetate/0-10% methanol as eluant. 124 mg of the title compound were obtained.

IR (film): 3420, 2730, 2670,1740, 1710, 1075, 975/cm.

k) (13E)-(8R,9S,11R,12R,15R)-9-benzoyloxy-16,16,19-trimethyl-15-hydroxy-11-(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

In the sodium borohydride reduction of the ketone according to f), in addition to the 2.02 g of α-alcohol and 0.7 g of an α/β mixture, 4.28 g of the title compound were eluted from the column as a less polar product.

IR (film): 3400 (broad), 1740, 1720, 1600, 1575, 1275, 1120, 1030, 1020, 710/cm.

l) (13E)-(8R,9S,11R,12R,15R)-9-benzoyloxy-16,16,19-trimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid methyl ester

Analogously to the method described in g) for the preparation of the 15α-isomer, 4.3 g of the title compound were obtained as a colourless oil by reacting 4.28 g of the alcohol obtained in the preceding reaction step with 0.96 ml of dihydropyran and 11 mg of p-toluenesulphonic acid (reaction time: 75 minutes) and after column chromatography over silica gel with ethyl acetate/hexane=1/3 as eluant.

IR (film): 1740, 1720, 1600, 1585, 1275, 1115, 1075, 1020, 715/cm.

m) (13E)-(8R,9S,11R,12R,15R)-9-hydroxy-16,16,19-trimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid

Analogously to the method described for the preparation of the 15α-isomer in h), 2.8 g of the title compound were obtained by reacting 4.3 g of the compound obtained in l) with 38.5 ml of 2N potassium hydroxide solution and after column chromatography over silica gel with hexane/50-100% ethyl acetate as eluant.

IR (film): 3450, 2730, 2660, 1730, 1710, 1130, 1110, 1075, 1025, 810/cm.

n) (13E)-(8R,11R,12R,15R)-9-oxo-16,16,19-trimethyl-11,15-bis(tetrahydropyran-2-yloxy)-13,18-prostadienoic acid

500 mg of the alcohol obtained in the preceding reaction

step were reacted analogously to the method described for the preparation of the corresponding 15α-isomer in i). 410 mg of the title compound were obtained.
IR (film): 2730, 2670, 1740, 1710, 1110, 1075, 1020, 810/cm.

o) (13E)-(8R,11R, 12R,15R)-11,15-dihydroxy-16,16,19-trimethyl-9-oxo-13,18-prostadienoic acid

Analogously to the method described for the synthesis of the 15β-isomer in j), 110 mg of the title compound were obtained by reacting 410 mg of the compound obtained in the preceding reaction step.
IR (film): 3400, 2730, 2660, 1740, 1710, 1075, 975/cm.

Example 3

(13E)-(8R,11R,12R,15S,16RS)-11,15-dihydroxy-16,19-dimethyl-9-oxo-13,18-prostadienoic acid. tris(hydroxymethyl)-aminomethane

A solution of 32.9 mg of tris(hydroxymethyl)-aminomethane in 0.1 ml of water was added at 60°C to a solution of 94.5 mg of the compound obtained according to Example 1 in 14 ml of acetonitrile. The mixture was left to stand at room temperature for 14 hours. The yield was 63.5 mg.

Example 4

(13E)-(8R,11R,12R,15R)-11,15-dihydroxy-16,16,19-trimethyl-9-oxo-13,18-prostadienoic acid. tris(hydroxymethyl)-aminomethane

Analogously to the method described in Example 3, 68.5 mg of the title compound were obtained from 98 mg of the compound

prepared according to Example 2.

Example 5

For use in parenteral administration the following solution was made up and filled into ampoules by conventional techniques.

0.5 mg of the compound obtained according to Example 1,

8.9 mg of NaCl,

1.212 mg of trometamol, and

0.01 ml of 96% strength ethanol

made up to 1 ml with water for injection.

Ampoules containing the compound obtained according to any one of Examples 2 to 4 were prepared in a similar manner.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

B

1. A process for the preparation of a (13E)-(8R, 11R, 12R)-11,15-dihydroxy-9-oxo-13,18-prostadienoic acid which is substituted at the 16-position by one or two methyl groups and at the 19-position by one methyl group, or a pharmaceutically acceptable salt thereof, which comprises reacting (8R,9S,11R,12S)-9-benzoyloxy-13-oxo-11-(tetrahydropyran-2-yl-oxy)-14,15,16,17,18,19,20-heptanorprostanoic methyl ester with either 2-(1,4-dimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester or 2-(1,1,4-trimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester, and then whichever of the following steps are necessary are carried out in any suitable order a) a free hydroxy group is protected; b) a protected hydroxy group is converted to a free hydroxy group; c) a 15-oxo-group is reduced; d) a 9-oxo group is reduced; e) a 9-hydroxy group is oxidised; f) an acid is converted into a pharmaceutically acceptable salt; g) a salt is converted into an acid; h) a salt is converted into another pharmaceutically salt; and i) a mixture of racemates is separated.

2. A process as claimed in claim 1, in which the reaction is effected at a temperature from 0 °C to 100°C in an aprotic solvent.

3. A process as claimed in claim 1, in which the reaction is effected at a temperature from 20°C to 80°C in an aprotic solvent selected from dimethyl sulphoxide, dimethylformamide, benzene, toluene, xylene, diethyl ether, tetrahydrofuran, dioxan, chloroform, methylene chloride and dimethoxyethane.

4. A process as claimed in claim 1, wherein 2-(1,4-dimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl

A

ester is reacted.

5. A process as claimed in claim 1, wherein 2-(1,1,4-trimethyl-3-pentenyl)-2-oxoethanephosphonic acid dimethyl ester is reacted.

6. A (13E)-(8R,11R,12R)-11,15-dihydroxy-9-oxo-13,18-prostadienoic acid which is substituted at the 16-position by one or two methyl groups and at the 19-position by one methyl group, or a pharmaceutically acceptable salt thereof, whenever prepared or produced by the process as claimed in claim 1, 2 or 3, or an obvious chemical equivalent thereof.

7. (13E)-(8R,11R,12R,15S,16RS)-11,15-dihydroxy-16,19-dimethyl-9-oxo-13,18-prostadienoic acid or a pharmaceutically acceptable salt thereof whenever prepared or produced by the process as claimed in claim 4, or an obvious chemical equivalent thereof.

8. (13E)-(8R,11R,12R,15R)-11,15-dihydroxy-16,16,19-trimethyl-9-oxo-13,18-prostadienoic acid or a pharmaceutically acceptable salt thereof whenever prepared or produced by the process as claimed in claim 5, or an obvious chemical equivalent thereof.

SUBSTITUTE

REMPLACEMENT

there are NO DRAWINGS

il n'y a PAS DE DESSINS